PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Watling *et al.*	)
	)
Application No.: 10/523,349	)
	)
Filed: 08/23/2005	)
	)
Group Art Unit: 1796	)
	)
Examiner: Marc S. Zimmer	)
	)
BIOMEDICAL COMPOSITIONS	)
	)
	)

DECLARATION OF TIMOTHY CHARLES HUGHES UNDER 37 C.F.R. § 1.132 ("HUGHES DECLARATION II")

I, Timothy Charles Hughes, of Bayview Avenue, Clayton, Victoria 3168, a principal research scientist, being duly warned hereby declare and state:

1. I am employed by Commonwealth Scientific and Industrial Research Organisation in the Molecular and Health Technologies Division as a principal research scientist. I was awarded a Doctor of Philosophy in 1997 in the field of Chemistry.

2. I have read and am familiar with:
   (a) the specification of US patent application no 10/523,349, and the International patent application from which it derives (**"the Present Application"**); and
   (b) U.S. patent no 6,737,496 to Hodd *et al* (**"the Pharmacia Patent"**).

3. I supervised, and was involved in, the synthesis and testing of the polysiloxane macromonomers and cured polymers which led to, and are used to exemplify, the Present Application. I am an inventor, and my employer is assignee, of the Present Application.

4. One of the primary objectives of our study was initially to synthesis a material suitable for use as a biological implant such as an intraocular lens (IOL) (ie a replacement for

the natural lens of the eye). One component of this was that the material should have mechanical properties that mimick that of the natural lens of the eye so, for example, that the ciliary muscles of the eye could manipulate the IOL as they would a natural IOL. The ciliary muscles serve the purpose of deforming the IOL to change the curvature, and thus the optical accommodating power (i.e. the ability to focus, in general terms), of the IOL. This was a significant challenge because, in 2002, all known materials suitable for IOL had a modulus orders of magnitude higher than the natural lens. Such a stiff material could not be sufficiently manipulated by the ciliary muscles. Various other implants and prostheses also require a similarly low modulus material.

5. The Pharmacia Patent states that the natural lens of the eye has a compression modulus of about 1 to 5 kPa (column 1 lines 41-42). However, it is not clear which modulus must have a value of about 1 to 5 kPa since the Pharmacia Patent refers to a compression modulus (column 1 lines 40-41, column 6 line 39) **and** shear modulus (column 10 lines 53-55, table at column 11). My own view, as set out below, is that it is the shear modulus that should be 1 to 5 kPa or even lower.

6. To try and understand the Pharmacia Patent, I have looked at what it describes. My understanding is that the materials of the Pharmacia Patent have been characterised using a rheometer. This is because the specification states at column 10 lines 29-55 that *"measurements of the shear (storage) modulus were then performed on the disks using a Rheometrics RDA2 rheometer"*. Thus, the values reported in the examples, and in particular the table at column 11, are shear moduli where the measurement is of the stress induced tangentially to the face of the material. Based on these demonstrated results, the materials of the Pharmacia Patent are stated as having shear moduli ranging from 21.0 – 65.3 kPa at 35 °C (table at column 11).

7. The Pharmacia Patent makes reference to a range of achievable moduli (column 6 lines 41-44). Here, it is stated that the materials of the Pharmacia Patent have a "modulus below about 55 kPa and in the range of 20 to 50 kPa". This range seems to

broadly coincide with the range 21.0 – 65.3 kPa reported in the examples suggesting they refer to a shear modulus, but there is no specific mention of the modulus being a shear modulus. To the contrary, the preceding sentence refers to a compression modulus (column 6 lines 37-41) stating *"by employing... material... of the present invention lenses with a compression modulus suitable to undergo accommodation... can be obtained"*. Despite this, it appears to me that this reference to 'compression modulus' is in error and the applicant clearly intended to refer to 'shear modulus'.

8. While compression modulus gives a good indication of the likely magnitude of the shear modulus, it is measured in a different manner from shear modulus in that a compression force is applied to the sample being measured, rather than an oscillating/twisting force.

9. Since the Pharmacia Patent is unclear to me, I have also reviewed the literature data available regarding the modulus of the natural lens of the eye. Although this data is not complete, and is complicated by various factors including the age of the test subject, pre-testing treatment conditions, and testing conditions, it is used in the field of synthesised lenses to provide a reliable indication of the mechanical properties of the natural lens of the eye. Presented in Table 1 below is data from a selection of literature references (which are attached).

TABLE 1

Reference	Species	Age (years)	n	Testing method	Minimum shear modulus (kPa)	Maximum shear modulus (kPa)
1	Human	0 - 67	40	Lens spinning	0.14	1.21
2	Human	14 - 76	18	DMA	0.05	2.58
3	Human	18 - 90	39	DMA	0.18	316.67
4	Cynomolgus Monkey		14	AFM	0.14	1.07
5	Porcine		4	Rheometry	0.01	

1 Fisher R., J Physiol, 1971, 212:147-80
2 Heys K., *et al.*, Molecular Vision, 2004, 10:956-63
3 Weeber H., *et al.*, Exp Eye Res., 2005, 80:425-34
4 Ziebarth N., *et al.*, Mol Vision, 2007, 13;504-10
5 Schachar *et al.*, Br J Ophthalmol., 2007, 91: 366-368
"n" is the number of samples tested
DMA is dynamic mechanical analysis
AFM is atomic force microscopy

10. The majority of data shows that the shear modulus of the natural lens of the eye is generally 0.05 to 2.8 kPa. The range claimed in the Present Application is 0.1 – 5 kPa. However, some data (such as reference no. 3 above) suggests the shear modulus of the natural lens of the eye may be much higher than 5 kPa. The reason for this higher value is as follows.

11. Measurement of the mechanical properties, and in particular the shear modulus, of the natural lens of the eye is difficult. There is no one agreed or accepted methodology for doing so. Some complicating factors related to the method of measurement include: (i) that after a natural lens is removed from the eye it is likely to harden over time and through handling (eg through dehydration and possibly by being frozen rather than fresh) thus increasing its modulus, (ii) different regions of the lens (eg the nucleus or cortex) have different moduli and it is not always clear which is being measured, (iii) that the modulus typically increases with age, hence reducing accommodative power

of the lens and lens available for measurement usually come from older people, (iv) that the lens capsule, a portion of which may remain during testing, has a modulus much higher than that of the lens material itself, (v) that in many cases, medications and disease cause hardening of the natural lens, and (vi) that the modulus as measured can also vary to some extent with the frequency (of oscillation) at which it is measured.

12. Thus, there is some debate in the literature as to the exact value of the shear modulus of a natural lens of the eye. As well, some data presents as significantly higher than other data due to the complicating factors mentioned above. For instance, in reference 3 the maximum shear modulus measured was 316.67 kPa. However, this data was obtained from an elderly human (90 years old) whose lens had likely hardened over the course of life. It was the maximum value of 39 lenses, the lowest being 0.18 kPa.

13. The desired modulus value (or range of values) for a synthetic IOL must be at the *lower* end of the range of measured natural lens moduli, which represent the properties of a *healthy* natural lens, which the ciliary muscles of the eye can manipulate to provide optical accommodation, before deterioration commences (usually at around the ages of 40 to 45). That is, the shear modulus of any replacement lens, despite the occasional out-lying data point, for an IOL capable of restoring or maintaining accommodation should clearly range from about 0.1 – 5 kPa.

14. The Pharmacia Patent therefore has not achieved the goal of having mechanical properties that mimic that of the natural lens of the eye. As mentioned above, the materials of the Pharmacia Patent are stated as having shear moduli ranging from 21.0 – 65.3 kPa at 35 °C (table at column 11). The Pharmacia Patent also does not provide instructions on how to achieve a material with a shear modulus within the range of from 0.1 to 5 kPa, despite indicating the desirability of doing so in the Background of the Invention at column 1 lines 39-42.

15. For some polymers of macromonomers (in some fields of application), a lower modulus may be achieved by reducing the functionalization per molecule (and so the degree of cross-linking). Additionally, a lower modulus may be achieved by increasing the chain length of the constituent macromonomers / molecules (when the degree of functionalization per molecule remains constant), but this effect is not predictable. However, for application as a biological implant, the task of reducing modulus is not as simple due to additional considerations such as injectability and biocompatibility. The inventors of the Present Application, arrived at a solution only through extensive study, insights and experimentation, and as described in the following paragraphs.

16. The macromonomers of the Present Application are administered in uncured form (usually by injection) and then cured (polymerised) *in vivo*. This imposes additional requirements that must be met by the polymer (i) the macromonomers of the uncured polymer must have sufficiently low viscosity that they can be injected into the eye using equipment sufficiently delicate for such a purpose (eg a needle with a bore of preferably less than 3mm); and (ii) the stiffness (as measured by the modulus) of the cured polymer must be sufficiently low to allow the lens to be manipulated by the ciliary muscles of the eye.

17. A further consideration is that of reducing undesirable biological reactions. One way to reduce undesirable biological reactions is to achieve a low or zero level of extractables (i.e. molecules that can leach out of the cured polymer) in the cured polymer. One way to reduce extractables is by having every macromonomer have at least one cross-link so that it becomes covalently bound during the polymerisation to another macromonomer. That is, the most obvious way known to the skilled person to achieve a low level of extractables in the cured polymer is to **increase the functionalization** per molecule.

18. A skilled person would expect to reduce the viscosity of the uncured composition by **reducing the length** of the macromonomers. Doing so however, will lead to an

increase in stiffness of the cured polymer assuming the same degree of functionalization per molecule and since every macromonomer has a cross-linked group (to avoid extractables). That is, the modulus is affected by the number of cross-links per unit length of macromonomer.

19. A skilled person would expect to reduce stiffness by **reducing the functionalization** per molecule (i.e. the opposite of that needed to achieve a low level of extractables in the cured polymer), and perhaps also by **increasing the length** (i.e. the opposite of that needed to achieve a low viscosity) of the macromonomers (while maintaining or reducing the degree of functionalization per molecule).

20. The skilled person is therefore directed in opposite directions, and the particular combinations that will work were far from obvious and were not predictable by a skilled person. Reaction kinetics and like practical challenges also arise.

21. The solution arrived at by my colleagues and I was the combined use of pendant and terminal functionalization. I currently believe that the degree of effect of terminal functionalization groups on the properties of the cured polymer differs from that for pendant functionalization groups. That is, by recognising that the location of the functionalization has a different effect on the cured polymer properties, we have discovered an additional variable by which to control the properties of the cured polymer to achieve the desired result (modulus from 0.1 to 5 kPa) but not achieved by the Pharmacia Patent. That is, using our invention, one is able to balance these competing considerations of viscosity, stiffness and amount of extractables.

22. The Pharmacia Patent does not contemplate nor teach the use of functionalization in the above manner. Although the Pharmacia Patent states that the cross-linkable groups may be pendant and/or terminal (col 4 line 1), there is no specific description in the specification of the Pharmacia Patent of polymers with pendant cross-linkable groups. For example, the structure at col 4 line 45 does not allow pendant cross-linkable groups and none of the examples demonstrate synthesis of polymers with pendant

cross-linkable groups.

23. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

By: _____

Timothy Charles Hughes

Date: 30th April 2008